EXHIBIT A
Pending Claims In Continuation

40. (Amended) A method for [identifying] binding a transforming growth factor β (TGF-β) protein in a sample, comprising contacting said sample with [an] a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide under conditions effective to allow binding [and detecting the protein so bound] of said LTBP-2 or LTBP-3 protein or polypeptide to said TGF-β protein; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

43. The method of claim 40, wherein said sample is located within an animal and said LTBP-2 or LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind TGF-β in said animal.

44. A method of binding TGF-β, comprising contacting a composition comprising TGF-β with a composition comprising a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

45. The method of claim 44, wherein said composition comprising TGF-β is located within an animal and said composition comprising said LTBP-2 or LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind TGF-β in said animal.

46. A method of using an LTBP-2 or LTBP-3 protein, polypeptide or peptide, comprising providing to an animal a biologically effective amount of a purified mammalian LTBP-2 or LTBP-3 protein, polypeptide or peptide that comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

47. The method of claim 46, wherein an amount of an LTBP-2 or LTBP-3 protein, polypeptide or peptide effective to generate anti-LTBP-2 or anti-LTBP-3 antibodies is provided to said animal.

48. The method of claim 47, wherein an LTBP-2 or LTBP-3 peptide of between 15 and about 50 amino acids in length is provided to said animal.

49. The method of claim 47, wherein an LTBP-2 or LTBP-3 peptide of between 15 and about 30 amino acids in length is provided to said animal.

50. The method of claim 47, wherein antisera comprising said anti-LTBP-2 or anti-LTBP-3 antibodies is collected from said animal.

51. The method of claim 46, wherein an amount of an LTBP-2 or LTBP-3 protein or polypeptide effective to bind TGF-β is provided to said animal.

52. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β regulates TGF-β activity in said animal.

53. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β modulates the activation of TGF-β in said animal.

54. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β modulates the activation of latent complexes that comprise TGF-β, thereby regulating TGF-β activity.

55. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the extracellular matrix in said animal.

56. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the bone matrix in said animal.

57. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to connective tissues in said animal.

58. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β targets TGF-β to the cell surface of cells in said animal.

59. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β protects TGF-β from proteolytic attack and activation in said animal.

60. The method of claim 51, wherein LTBP-2 or LTBP-3 binding to TGF-β protects TGF-β from proteolytic attack and activation during wound repair or tissue healing in said animal.

61. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide is a recombinant protein or polypeptide prepared by expressing an LTBP-2-encoding or LTBP-3-encoding DNA segment in a recombinant host cell and purifying the expressed LTBP-2 or LTBP-3 protein or polypeptide away from total recombinant host cell components.

62. The method of claim 51, wherein said TGF-β is located within a tissue healing, wound repair tissue site or bone progenitor tissue site of said animal and wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site.

63. The method of claim 62, wherein said TGF-β is located within a tissue healing or wound repair tissue site of said animal.

64. The method of claim 62, wherein said TGF-β is located within a bone progenitor tissue site of said animal.

65. The method of claim 62, wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site by contacting said tissue site with a composition comprising a nucleic acid segment that expresses said LTBP-2 or LTBP-3 protein or polypeptide in cells of said tissue site.

66. The method of claim 65, wherein said LTBP-2 or LTBP-3 protein or polypeptide is provided to said tissue site by contacting said tissue site with a composition comprising said nucleic acid segment and a structural biocompatible matrix.

67. The method of claim 65, wherein said nucleic acid segment is a DNA segment.

68. The method of claim 65, wherein said nucleic acid segment is an RNA segment.

69. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least about thirty contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

70. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least about fifty contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

71. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:4, respectively.

72. The method of claim 51, wherein said LTBP-2 or LTBP-3 protein or polypeptide exhibits between 91% and about 99% identity to the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:4, respectively.

73. The method of claim 51, wherein an LTBP-2 protein comprising the amino acid sequence of SEQ ID NO:2 is provided to said animal.

74. The method of claim 51, wherein an LTBP-3 protein comprising the amino acid sequence of SEQ ID NO:4 is provided to said animal.

75. A method of using an LTBP-2 or LTBP-3 protein or polypeptide, comprising administering to an animal a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide specifically binds TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

76. A method of binding TGF-β within a repair or bone progenitor tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide, or a nucleic acid that expresses said LTBP-2 or LTBP-3 protein or polypeptide, to provide an amount of said LTBP-2 or LTBP-3 protein or polypeptide effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

77. A method of binding TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-2 or LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-2 or LTBP-3 protein or polypeptide comprises at least fifteen contiguous amino acids present in SEQ ID NO:2 or SEQ ID NO:4, respectively.

78. A method of binding TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds TGF-β and comprises at least fifteen contiguous amino acids present in SEQ ID NO:4 or exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4.

EXHIBIT B
Allowed Claims in Parent, Serial No. 08/479,722

127. An isolated nucleic acid molecule comprising a sequence encoding at least fifteen contiguous amino acids present in SEQ ID NO:4.

128. The isolated nucleic acid molecule of claim 127, comprising a sequence that encodes at least about thirty contiguous amino acids present in SEQ ID NO:4.

129. The isolated nucleic acid molecule of claim 127, comprising a sequence that encodes at least about fifty contiguous amino acids present in SEQ ID NO:4.

130. The isolated nucleic acid molecule of claim 127, comprising a sequence which, upon translation, affords a peptide of between 15 and about 50 amino acids in length.

131. The isolated nucleic acid molecule of claim 127, comprising a sequence which, upon translation, affords a peptide of between 15 and about 30 amino acids in length.

132. The isolated nucleic acid molecule of claim 127, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 1, domain 2, domain 3, domain 4 or domain 5 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

133. The isolated nucleic acid molecule of claim 132, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 1 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

134. The isolated nucleic acid molecule of claim 132, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 2 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

135. The isolated nucleic acid molecule of claim 132, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 3 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

136. The isolated nucleic acid molecule of claim 132, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 4 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

137. The isolated nucleic acid molecule of claim 132, comprising a sequence that encodes a polypeptide or peptide in which said at least fifteen contiguous amino acids present in SEQ ID NO:4 are present in domain 5 of the LTBP-3 polypeptide sequence set forth in SEQ ID NO:4.

138. The isolated nucleic acid molecule of claim 127, comprising a sequence that encodes a polypeptide comprising about 1,251 contiguous amino acids in SEQ ID NO:4.

140. (Amended) The isolated nucleic acid molecule of claim 138, comprising the contiguous nucleic acid sequence of SEQ ID NO:3.

141. The isolated nucleic acid molecule of claim 127, further comprising a recombinant promoter.

142. The isolated nucleic acid molecule of claim 141, wherein said sequence is positioned, in reverse orientation, under the control of a promoter that directs the expression of an antisense product.

143. The isolated nucleic acid molecule of claim 127, further defined as a recombinant vector.

144. An isolated nucleic acid molecule comprising a sequence that encodes a protein having the contiguous amino acid sequence of SEQ ID NO:4.

145. An isolated nucleic acid molecule encoding a polypeptide that exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4, wherein said polypeptide specifically binds to TGF-β1.

146. The isolated nucleic acid molecule of claim 145, wherein the encoded polypeptide exhibits between 91% and about 99% identity to the amino acid sequence set forth in SEQ ID NO:4.

147. An isolated nucleic acid molecule encoding a mammalian LTBP-3 polypeptide, wherein said nucleic acid molecule comprises the nucleotide sequence of:

(a) the coding sequence of a cDNA molecule present in a mammalian library, wherein the cDNA molecule hybridizes with a probe having the sequence of the complement of SEQ ID NO:3 under conditions of high stringency; or

(b) a nucleotide sequence degenerate with a sequence according to (a).

148. The isolated nucleic acid molecule of claim 147, wherein said nucleic acid molecule comprises the nucleotide sequence of the coding sequence of a cDNA molecule present in a mammalian library, wherein the cDNA molecule hybridizes with a probe having the sequence of the complement of SEQ ID NO:3 under conditions of high stringency.

149. The isolated nucleic acid molecule of claim 147, wherein said nucleic acid molecule comprises a nucleotide sequence degenerate with the coding sequence of a cDNA molecule present in a mammalian library, wherein the cDNA molecule hybridizes with a probe having the sequence of the complement of SEQ ID NO:3 under conditions of high stringency.

152. (Amended) The isolated nucleic acid molecule of claim 147, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 50 contiguous nucleotides present in SEQ ID NO:3.

153. The isolated nucleic acid molecule of claim 152, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 100 contiguous nucleotides present in SEQ ID NO:3.

154. The isolated nucleic acid molecule of claim 153, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 200 contiguous nucleotides present in SEQ ID NO:3.

155. The isolated nucleic acid molecule of claim 154, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 500 contiguous nucleotides present in SEQ ID NO:3.

156. The isolated nucleic acid molecule of claim 155, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 1000 contiguous nucleotides present in SEQ ID NO:3.

157. The isolated nucleic acid molecule of claim 156, wherein the nucleic acid molecule comprises a nucleotide sequence of at least 3000 contiguous nucleotides present in SEQ ID NO:3.

159. The isolated nucleic acid molecule of claim 147, wherein the nucleic acid molecule is up to about 10,000 basepairs in length.

160. The isolated nucleic acid molecule of claim 159, wherein the nucleic acid molecule is up to about 5,000 basepairs in length.

161. The isolated nucleic acid molecule of claim 147, further defined as a DNA molecule.

162. The isolated nucleic acid molecule of claim 147, further defined as an RNA molecule.

163. An isolated nucleic acid molecule encoding a mammalian LTBP-3 polypeptide, wherein said nucleic acid molecule comprises the nucleotide sequence of

(a) the coding sequence of a cDNA molecule present in a mammalian library, wherein the cDNA molecule hybridizes, under conditions of high stringency, with a probe having the sequence of the complement of the isolated LTBP-3 sequence region within the biological material deposited as ATCC 209496; or

(b) a nucleotide sequence degenerate with a sequence according to (a).

164. (Amended) The isolated nucleic acid molecule of claim 163, wherein said nucleic acid molecule [encodes a mammalian LTBP-3 polypeptide that includes at least fifteen contiguous amino acids encoded by] comprises a sequence of at least 50 contiguous nucleotides present in the sequence of the isolated LTBP-3 sequence region within the biological material deposited as ATCC 209496.

165. The isolated nucleic acid molecule of claim 164, wherein said nucleic acid molecule encodes a mammalian LTBP-3 polypeptide that comprises about 1,251 contiguous amino acids encoded by the isolated LTBP-3 sequence region within the biological material deposited as ATCC 209496.

166. The isolated nucleic acid molecule of claim 165, wherein said nucleic acid molecule has the nucleotide sequence of the isolated LTBP-3 sequence region within the biological material deposited as ATCC 209496.

167. (Amended) An isolated nucleic acid molecule encoding a mammalian LTBP-3 polypeptide, wherein said nucleic acid molecule comprises the nucleotide sequence of

> the coding sequence of a cDNA molecule present in a mammalian library, wherein the cDNA molecule hybridizes, under conditions of high stringency, with a probe having the sequence of the complement of the isolated LTBP-3 sequence region within the vector pLTBP-3fl, deposited as ATCC 209496.

168. The isolated nucleic acid molecule of claim 167, wherein said nucleic acid molecule encodes a mammalian LTBP-3 polypeptide that has the contiguous amino acid sequence encoded by the isolated LTBP-3 sequence region within the vector pLTBP-3fl.

169. A recombinant host cell comprising an isolated nucleic acid molecule in accordance with claim 127, claim 144, claim 145, claim 147, claim 163 or claim 167.

170. The recombinant host cell of claim 169, further defined as a prokaryotic host cell.

171. The recombinant host cell of claim 169, further defined as a eukaryotic host cell.

172. The recombinant host cell of claim 169, wherein the isolated nucleic acid molecule is introduced into the cell by means of a recombinant vector and the host cell expresses the isolated nucleic acid molecule to produce the encoded protein or peptide.

173. (Amended) A method of using an isolated nucleic acid molecule that encodes a protein or peptide, the method comprising expressing, in a recombinant host cell, a recombinant vector that comprises an isolated nucleic acid molecule in accordance with claim 127, claim 144, claim 145, claim 147, claim 163 or claim 167, and collecting the expressed protein or peptide.

EXHIBIT C
Claims Restricted from Parent, Serial No. 08/479,722

Group III:
22. A recombinant LTBP-2 or LTBP-3 protein or peptide prepared by expressing an LTBP-2- or LTBP-3-encoding DNA segment in a recombinant host cell and purifying the expressed LTBP-2- or LTBP-3 protein or peptide away from total recombinant host cell components.

42. A composition comprising a purified murine LTBP-2 or LTBP-3 polypeptide.

Part of Group IV
23. A method for detecting an LTBP-2 or LTBP-3 nucleic acid segment in a sample, comprising the steps of:

(a) obtaining sample nucleic acids from a sample suspected of containing an LTBP-2 or LTBP-3 nucleic acid segment;

(b) contacting said sample nucleic acids with an isolated LTBP-2 or LTBP-3 nucleic acid segment under conditions effective to allow hybridization of substantially complementary nucleic acids; and

(c) detecting the hybridized complementary nucleic acids thus formed.

Group V:
37. A purified antibody that binds to an LTBP-3 protein or peptide.

38. The antibody of claim 37, wherein the antibody is linked to a detectable label.

39. An immunodetection kit comprising, in suitable container means, an LTBP-3 protein or peptide, or a first antibody that binds to an LTBP-3 protein or peptide, and an immunodetection reagent.

Group VI:
40. A method for identifying a transforming growth factor β protein in a sample, comprising contacting said sample with an LTBP-2 or LTBP-3 protein under conditions effective to allow binding and detecting the protein so bound.

41. A method for purifying transforming growth factor β (TGFβ) protein in a sample, comprising:

(a) contacting a sample suspected of containing TGFβ β protein with an LTBP-2 or LTBP-3 protein under conditions effective to allow specific binding; and

(b) collecting the bound TGFβ, substantially free from the non-bound components.

EXHIBIT D
Claims to Issue in Grandparent, Patent No. 5,942,496

51. (Amended) A method for transferring nucleic acid segments into bone progenitor cells located within a bone progenitor tissue site of an animal, comprising contacting said tissue site with a composition comprising two or more nucleic acid segments and a structural bone-compatible matrix, so as to transfer said two or more nucleic acid segments into said cells, wherein said cells express transcriptional or translational products encoded by said nucleic acid segments.

52. (Amended) The method of claim 51, comprising contacting bone progenitor cells with a composition comprising two nucleic acid segments and a structural bone-compatible matrix.

53. (Amended) The method of claim 51, comprising contacting bone progenitor cells with a composition comprising three nucleic acid segments and a structural bone-compatible matrix.

55. (Amended) The method of claim 51, wherein the contacting process comprises bringing said two or more nucleic acid segments into contact with said structural bone-compatible matrix to form a matrix-nucleic acid segments composition and bringing said matrix-nucleic acid segments composition into contact with said tissue site.

56. (Amended) The method of claim 55, wherein said nucleic acid segments are absorbed in said structural bone-compatible matrix.

57. (Amended) The method of claim 55, wherein said nucleic acid segments are adsorbed to said structural bone-compatible matrix.

58. (Amended) The method of claim 55, wherein said nucleic acid segments are impregnated within said structural bone-compatible matrix.

59. The method of claim 51, wherein said bone progenitor cells are stem cells, macrophages, fibroblasts, vascular cells, osteoblasts, chondroblasts or osteoclasts.

60. The method of claim 59, wherein said bone progenitor cells are fibroblasts.

61. The method of claim 51, wherein at least one of said two or more nucleic acid segments is a DNA molecule.

62. (Amended) The method of claim 51, wherein at least one of said two or more nucleic acid segments is an antisense nucleic acid molecule.

63. The method of claim 51, wherein at least one of said two or more nucleic acid segments is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

64. (Amended) The method of claim 51, wherein at least one of said two or more nucleic acid segments encodes a polypeptide or protein that stimulates bone progenitor cells when expressed by said cells.

65. (Amended) The method of claim 51, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

66. (Amended) The method of claim 65, wherein said structural bone-compatible matrix is a titanium matrix.

67. (Amended) The method of claim 66, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

68. (Amended) The method of claim 65, wherein said structural bone-compatible matrix is a collagen preparation.

69. (Amended) The method of claim 68, wherein said structural bone-compatible matrix is a type II collagen preparation.

70. (Amended) The method of claim 69, wherein said structural bone-compatible matrix is a recombinant type II collagen preparation.

71. (Amended) The method of claim 69, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with minerals.

72. (Amended) The method of claim 65, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

73. (Amended) A method of stimulating bone progenitor cells located within a bone progenitor tissue site of an animal, comprising contacting said tissue site with a composition comprising two or more osteotropic genes and a structural bone-compatible matrix so as to promote expression of said genes by said cells.

74. (Amended) The method of claim 73, comprising contacting said tissue site with a composition comprising two osteotropic genes and a structural bone-compatible matrix.

75. (Amended) The method of claim 73, comprising contacting said tissue site with a composition comprising three osteotropic genes and a structural bone-compatible matrix.

76. (Amended) The method of claim 73, wherein expression of said osteotropic genes by said cells stimulates said cells to promote bone tissue growth.

77. (Amended) The method of claim 73, wherein the contacting process comprises bringing said osteotropic genes into contact with said structural bone-compatible matrix to form a matrix-genes composition and bringing said matrix-genes composition into contact with said tissue site.

78. (Amended) The method of claim 73, wherein said osteotropic genes are absorbed in said structural bone-compatible matrix.

79. (Amended) The method of claim 73, wherein said osteotropic genes are adsorbed in said structural bone-compatible matrix.

80. (Amended) The method of claim 73, wherein said osteotropic genes are impregnated within said structural bone-compatible matrix.

81. The method of claim 73, wherein said bone progenitor cells are stem cells, macrophages, fibroblasts, vascular cells, osteoblasts, chondroblasts or osteoclasts.

82. The method of claim 81, wherein said bone progenitor cells are fibroblasts.

83. The method of claim 73, wherein at least one of said two or more osteotropic genes is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

84. The method of claim 73, wherein at least one of said two osteotropic genes is a parathyroid hormone (PTH) gene, a bone morphogenetic protein (BMP) gene, a growth factor gene, a growth factor receptor gene, a cytokine gene or a chemotactic factor gene.

85. (Amended) The method of claim 84, wherein at least one of said two osteotropic genes is a transforming growth factor (TGF) gene, a fibroblast growth factor (FGF) gene, a granulocyte/macrophage colony stimulating factor (GMCSF) gene, an epidermal growth factor (EGF) gene, a platelet derived growth factor (PDGF) gene, an insulin-like growth factor (IGF) gene, a latent TGF-β binding protein (LTBP) gene or a leukemia inhibitory factor (LIF) gene.

86. (Amended) The method of claim 85, wherein at least one of said two or more osteotropic genes is a TGF-α, TGF-β1 or TGF-β2 gene.

87. The method of claim 84, wherein at least one of said two osteotropic genes is a PTH gene.

88. The method of claim 84, wherein at least one of said two osteotropic genes is a BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 gene.

89. The method of claim 84, wherein at least one of said two osteotropic genes is a PTH1-34 gene, a BMP-2 gene or a BMP-4 gene.

90. The method of claim 84, wherein said composition comprises a PTH gene and a BMP gene.

91. The method of claim 90, wherein said composition comprises a PTH1-34 gene and a BMP-4 gene.

92. (Amended) The method of claim 73, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

93. (Amended) The method of claim 92, wherein said structural bone-compatible matrix is a titanium matrix.

94. (Amended) The method of claim 93, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

95. (Amended) The method of claim 92, wherein said structural bone-compatible matrix is a collagen preparation.

96. (Amended) The method of claim 95, wherein said structural bone-compatible matrix is a type II collagen preparation.

97. (Amended) The method of claim 96, wherein said structural bone-compatible matrix is a recombinant type II collagen preparation.

98. (Amended) The method of claim 96, wherein said structural bone-compatible matrix is a mineralized type II collagen preparation.

99. (Amended) The method of claim 92, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

100. (Amended) The method of claim 73, wherein said composition is applied to a bone fracture site in said animal.

101. (Amended) The method of claim 73, wherein said composition is implanted within a bone cavity site in said animal.

102. The method of claim 101, wherein said bone cavity site is the result of dental or periodontal surgery or the removal of an osteosarcoma.

103. (Amended) A method of delivering two or more nucleic acid segments to a fibroblast cell located within a repair tissue site of an animal, comprising contacting said tissue site with a composition comprising two or more nucleic acid segments and a structural bone-compatible matrix to effect uptake of the nucleic acid segments into the fibroblast cell and to promote expression of transcriptional or translational products by said fibroblast cell.

104. (Amended) A method of delivering two or more selected nucleic acid segments to a fibroblast cell located within a repair tissue site of an animal, comprising the steps of:

(a) preparing a matrix-nucleic acid composition comprising two or more nucleic acid segments and a structural bone-compatible matrix; and

(b) contacting said repair tissue site with the structural matrix-nucleic acid composition to effect uptake of the nucleic acid segments by the fibroblast cell, wherein said fibroblast cell expresses transcriptional or translational products encoded by said nucleic acid segments.

105. (Amended) The method of claim 104, wherein step (a) comprises preparing a matrix-nucleic acid composition comprising two nucleic acid segments and a structural bone-compatible matrix.

106. (Amended) The method of claim 104, wherein step (a) comprises preparing a matrix-nucleic acid composition comprising three nucleic acid segments and a structural bone-compatible matrix.

108. (Amended) The method of claim 104, wherein said nucleic acid segments are absorbed in or adsorbed to said structural bone-compatible matrix.

109. (Amended) The method of claim 104, wherein said nucleic acid segments are impregnated within said structural bone-compatible matrix.

110. The method of claim 104, wherein at least one of said two or more nucleic acid segments is a DNA molecule.

111. The method of claim 104, wherein at least one of said two or more nucleic acid segments is an RNA molecule.

112. (Amended) The method of claim 104, wherein at least one of said two or more nucleic acid segments is an antisense nucleic acid molecule.

113. The method of claim 104, wherein at least one of said two or more nucleic acid segments is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

114. The method of claim 104, wherein at least one of said two or more nucleic acid segments is an osteotropic gene.

115. The method of claim 114, wherein at least one said osteotropic genes is a parathyroid hormone (PTH) gene, a bone morphogenetic protein (BMP) gene, a growth factor gene, a growth factor receptor gene, a cytokine gene or a chemotactic factor gene.

116. (Amended) The method of claim 115, wherein at least one of said osteotropic genes is a transforming growth factor (TGF) gene, a fibroblast growth factor (FGF) gene, a granulocyte/macrophage colony stimulating factor (GMCSF) gene, an epidermal growth factor (EGF) gene, a platelet derived growth factor (PDGF) gene, an insulin-like growth factor (IGF) gene, a latent TGF-β binding protein (LTBP) gene or a leukemia inhibitory factor (LIF) gene.

117. The method of claim 116, wherein at least one of said osteotropic genes is a TGF-α, TGF-β1 or TGF-β2 gene.

118. The method of claim 115, wherein at least one of said osteotropic genes is a PTH gene.

119. The method of claim 118, wherein at least one of said osteotropic genes is a PTH1-34 gene.

120. The method of claim 115, wherein at least one of said osteotropic genes is a BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 gene.

121. The method of claim 120, wherein at least one of said osteotropic genes is a BMP-2 or BMP-4 gene.

122. The method of claim 115, wherein said matrix-nucleic acid composition comprises a PTH gene and a BMP gene.

123. The method of claim 122, wherein said matrix-nucleic acid composition comprises a PTH1-34 gene and a BMP-4 gene.

124. (Amended) The method of claim 104, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, hydroxylapatite-coated metal, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

125. (Amended) The method of claim 124, wherein said structural bone-compatible matrix is a titanium matrix.

126. (Amended) The method of claim 125, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

127. (Amended) The method of claim 124, wherein said structural bone-compatible matrix is a collagen preparation.

128. (Amended) The method of claim 127, wherein said structural bone-compatible matrix is a type II collagen preparation.

129. (Amended) The method of claim 128, wherein said structural bone-compatible matrix is a recombinant type II collagen preparation.

130. (Amended) The method of claim 128, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with minerals.

131. (Amended) The method of claim 124, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

132. (Amended) A composition comprising two or more nucleic acid segments in association with a structural bone-compatible matrix.

133. (Amended) The composition of claim 132, wherein said composition comprises two nucleic acid segments in association with said structural bone-compatible matrix.

134. (Amended) The composition of claim 132, wherein said composition comprises three nucleic acid segments in association with said structural bone-compatible matrix.

135. (Amended) The composition of claim 132, wherein said nucleic acid segments are absorbed in or adsorbed to said structural bone-compatible matrix.

136. (Amended) The composition of claim 132, wherein said nucleic acid segments are impregnated within said structural bone-compatible matrix.

137. The composition of claim 132, wherein at least one of said two or more nucleic acid segments is a DNA molecule.

138. The composition of claim 132, wherein at least one of said two or more nucleic acid segments is an RNA molecule.

139. The composition of claim 132, wherein at least one of said two or more nucleic acid segments is an antisense nucleic acid molecule.

140. The composition of claim 132, wherein at least one of said two or more nucleic acid segments is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

141. (Amended) The composition of claim 132, wherein at least one of said two or more nucleic acid segments encodes a polypeptide or protein that stimulates bone progenitor cells when expressed by said cells.

142. (Amended) The composition of claim 132, wherein said structural bone-compatible matrix is a collagenous, titanium, hydroxylapatite, hydroxylapatite-coated titanium, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

143. (Amended) The composition of claim 142, wherein said structural bone-compatible matrix is a collagen preparation.

144. (Amended) The composition of claim 143, wherein said structural bone-compatible matrix is a type II collagen preparation.

145. (Amended) The composition of claim 144, wherein said structural bone-compatible matrix is a recombinant type II collagen preparation.

146. (Amended) The composition of claim 144, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with minerals.

147. (Amended) The composition of claim 146, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with calcium.

148. (Amended) The composition of claim 142, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

149. (Amended) A composition comprising two or more osteotropic genes in association with a structural bone-compatible matrix, said composition being capable of stimulating bone growth when administered to a bone progenitor tissue site of an animal.

150. (Amended) The composition of claim 149, wherein said composition comprises two osteotropic genes in association with said structural bone-compatible matrix.

151. (Amended) The composition of claim 149, wherein said composition comprises three osteotropic genes in association with said structural bone-compatible matrix.

152. (Amended) The composition of claim 149, wherein said osteotropic genes are absorbed in or adsorbed to said structural bone-compatible matrix.

153. (Amended) The composition of claim 149, wherein said osteotropic genes are impregnated within said structural bone-compatible matrix.

154. The composition of claim 149, wherein at least one of said two or more osteotropic genes is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

155. (Amended) The composition of claim 149, wherein at least one of said two or more osteotropic genes is a PTH, BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, TGF-α, TGF-β1, TGF-β2, FGF, GMCSF, EGF, PDGF, IGF, LTBP or a LIF gene.

156. (Amended) The composition of claim 155, wherein at least one of said osteotropic genes is a TGF-α, TGF-β1, TGF-β2, PTH, LTBP, BMP-2 or BMP-4 gene.

157. The composition of claim 155, wherein at least one of said osteotropic genes is a PTH gene.

158. The composition of claim 157, wherein at least one of said osteotropic genes is a PTH1-34 gene.

159. The composition of claim 155, wherein at least one of said osteotropic genes is a BMP-2 or BMP-4 gene.

160. The composition of claim 155, wherein said composition comprises a PTH gene and a BMP gene.

161. The composition of claim 160, wherein said composition comprises a PTH1-34 gene and a BMP-4 gene.

162. (Amended) The composition of claim 149, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxyapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

163. (Amended) The composition of claim 162, wherein said structural bone-compatible matrix is a titanium matrix.

164. (Amended) The composition of claim 163, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

165. (Amended) The composition of claim 162, wherein said structural bone-compatible matrix is a collagen preparation.

166. (Amended) The composition of claim 165, wherein said structural bone-compatible matrix is a type II collagen preparation.

167. (Amended) The composition of claim 166, wherein said structural bone-compatible matrix is a recombinant type II collagen preparation.

168. (Amended) The composition of claim 166, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with minerals.

169. (Amended) The composition of claim 168, wherein said structural bone-compatible matrix is a type II collagen preparation further supplemented with calcium.

170. (Amended) The composition of claim 162, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

171. (Amended) An osteotropic device, comprising two or more osteotropic genes capable of expression by bone progenitor cells, the genes associated with an amount of a structural bone-compatible matrix effective to absorb or adsorb said genes, wherein said device is capable of stimulating bone formation when implanted within a bone progenitor tissue site of an animal.

172. The device of claim 171, wherein said device comprises three or more osteotropic genes.

173. The device of claim 171, wherein said device is a titanium or a hydroxylapatite-coated titanium device.

174. The device of claim 171, wherein said device is shaped to join a bone fracture site in said animal.

175. The device of claim 171, wherein said device is shaped to fill a bone cavity site in said animal.

176. The device of claim 171, wherein said device is an artificial joint.

177. The method of claim 51, wherein at least one of said two or more nucleic acid segments is an RNA molecule.

178. The method of claim 85, wherein at least one of said two or more osteotropic genes is an LTBP gene.

179. The method of claim 116, wherein at least one of said osteotropic genes is an LTBP gene.

180. The device of claim 171, wherein said device comprises a PTH, BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, TGF-α, TGF-β1, TGF-β2, FGF, GMCSF, EGF, PDGF, IGF, LTBP or a LIF gene.

181. The device of claim 180, wherein said device comprises a TGF-α, TGF-β1, TGF-β2, PTH1-34, LTBP, BMP-2 or BMP-4 gene.

182. The device of claim 180, wherein said device comprises a PTH gene and a BMP gene.

EXHIBIT E
Issued Claims in Great Grandparent, Patent No. 5,763,416

1. A method for transferring a nucleic acid segment into bone progenitor cells located within a bone progenitor tissue site of an animal, comprising contacting said tissue site with a composition comprising a nucleic acid segment and a structural bone-compatible matrix so as to transfer said nucleic acid segment into said cells, wherein said nucleic acid segment expresses a transcriptional or translational product in said cells.

2. The method of claim 1, wherein the contacting process comprises bringing said nucleic acid segment into contact with said structural bone-compatible matrix to form a matrix-nucleic acid segment composition and bringing said matrix-nucleic acid segment composition into contact with said tissue site.

3. The method of claim 2, wherein said nucleic acid segment is absorbed in said structural bone-compatible matrix.

4. The method of claim 2, wherein said nucleic acid segment is adsorbed to said structural bone-compatible matrix.

5. The method of claim 2, wherein said nucleic acid segment is impregnated within said structural bone-compatible matrix..

6. The method of claim 1, wherein said nucleic acid segment is a DNA molecule.

7. The method of claim 1, wherein said nucleic acid segment is an RNA molecule.

8. The method of claim 1, wherein said nucleic acid segment is an antisense nucleic acid molecule.

9. The method of claim 1, wherein said nucleic acid segment is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

10. The method of claim 1, wherein said nucleic acid segment encodes a polypeptide or protein that stimulates bone progenitor cells when expressed in said cells.

11. The method of claim 1, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

12. The method of claim 11, wherein said structural bone-compatible matrix is a titanium matrix.

13. The method of claim 12, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

14. The method of claim 11, wherein said bone-compatible matrix is a collagen preparation.

15. The method of claim 11, wherein said bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

16. The method of claim 1, wherein said bone progenitor cells are stem cells, macrophages, fibroblasts, vascular cells, osteoblasts, chondroblasts or osteoclasts.

17. The method of claim 16, wherein said bone progenitor cells are fibroblasts.

18. A method of stimulating bone progenitor cells located within a bone progenitor tissue site of an animal, comprising contacting said tissue site with a composition comprising an osteotropic gene and a structural bone-compatible matrix so as to promote expression of said gene in said cells.

19. The method of claim 18, wherein expression of said gene in said cells stimulates said cells to promote bone tissue growth.

20. The method of claim 18, wherein the contacting process comprises bringing said osteotropic gene into contact with said structural bone-compatible matrix to form a matrix-gene composition and bringing said matrix-gene composition into contact with said tissue site.

21. The method of claim 20, wherein said nucleic acid segment is absorbed in said structural bone-compatible matrix.

22. The method of claim 20, wherein said nucleic acid segment is adsorbed to said structural bone-compatible matrix.

23. The method of claim 20, wherein said nucleic acid segment is impregnated within said structural bone-compatible matrix.

24. The method of claim 18, wherein said osteotropic gene is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

25. The method of claim 18, wherein said osteotropic gene is a parathyroid hormone (PTH) gene, a bone morphogenetic protein (BMP) gene, a growth factor gene, a growth factor receptor gene, a cytokine gene or a chemotactic factor gene.

26. The method of claim 25, wherein said osteotropic gene is a transforming growth factor (TGF) gene, a fibroblast growth factor (FGF) gene, a granulocyte/macrophage colony stimulating factor (GMCSF) gene, an epidermal growth factor (EGF) gene, a platelet derived growth factor (PDGF) gene, an insulin-like growth factor (IGF) gene, or a leukemia inhibitory factor (LIF) gene.

27. The method of claim 26, wherein said osteotropic gene is a TGF-α, TGF-β1 or TGF-β2 gene.

28. The method of claim 25, wherein said osteotropic gene is a PTH gene.

29. The method of claim 28, wherein said osteotropic gene is a PTH1-34.

30. The method of claim 25, wherein said osteotropic gene is a BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 gene.

31. The method of claim 30, wherein said osteotropic gene is a BMP-2 or BMP-4 gene.

32. The method of claim 18, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

33. The method of claim 32, wherein said structural bone-compatible matrix is a titanium matrix.

34. The method of claim 33, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

35. The method of claim 32, wherein said structural bone-compatible matrix is a collagen preparation.

36. The method of claim 32, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

37. The method of claim 19, wherein said matrix-gene composition is applied to a bone fracture site in said animal.

38. The method of claim 19, wherein said matrix-gene composition is implanted within a bone cavity site in said animal.

39. The method of claim 38, wherein said bone cavity site is the result of dental or periodontal surgery or the removal of an osteosarcoma.

40. The method of claim 18, wherein said bone progenitor cells are stem cells, macrophages, fibroblasts, vascular cells, osteoblasts, chondroblasts or osteoclasts.

41. The method of claim 40, wherein said bone progenitor cells are fibroblasts.

42. A composition comprising a nucleic acid segment in association with a structural bone-compatible matrix.

43. The composition of claim 42, wherein said nucleic acid segment is absorbed in said structural bone-compatible matrix.

44. The composition of claim 42, wherein said nucleic acid segment is adsorbed to said structural bone-compatible matrix.

45. The composition of claim 42, wherein said nucleic acid segment is impregnated within said structural bone-compatible matrix.

46. The composition of claim 42, wherein said nucleic acid segment is a DNA molecule.

47. The composition of claim 42, wherein said nucleic acid segment is an RNA molecule.

48. The composition of claim 42, wherein said nucleic acid segment is an antisense nucleic acid molecule.

49. The composition of claim 42, wherein said nucleic acid segment is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

50. The composition of claim 42, wherein said nucleic acid segment encodes a polypeptide or protein that stimulates bone progenitor cells when expressed in said cells.

51. The composition of claim 42, wherein said structural bone-compatible matrix is a collagenous, titanium, hydroxylapatite, hydroxylapatite-coated titanium, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

52. The composition of claim 51, wherein said structural bone-compatible matrix is a collagen preparation.

53. The composition of claim 51, wherein said bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

54. A composition comprising an osteotropic gene in association with a bone-compatible matrix, said composition being capable of stimulating bone growth when administered to a bone progenitor tissue site of an animal.

55. The composition of claim 54, wherein said osteotropic gene is absorbed in said structural bone-compatible matrix.

56. The composition of claim 54, wherein said osteotropic gene is adsorbed to said structural bone-compatible matrix.

57. The composition of claim 54, wherein said osteotropic gene is impregnated within said structural bone-compatible matrix.

58. The composition of claim 54, wherein said osteotropic gene is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

59. The composition of claim 54, wherein said osteotropic gene is a PTH, BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, TGF-α, TGF-β1, TGF-β2, FGF, GMCSF, EGF, PDGF, IGF or a LIF gene.

60. The composition claim 59, wherein said osteotropic gene is a TGF-α, TGF-β1, TGF-β2, PTH, BMP-2 or BMP-4 gene.

61. The composition of claim 60, wherein said osteotropic gene is a PTH1-34 gene.

62. The composition of claim 54, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxyapatite, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

63. The composition of claim 62, wherein said structural bone-compatible matrix is a titanium matrix.

64. The composition of claim 63, wherein said structural bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

65. The composition of claim 62, wherein said structural bone-compatible matrix is a collagen preparation.

66. The composition of claim 62, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

67. An osteotropic device, comprising an osteotropic gene capable of expression in bone progenitor cells, the gene associated with an amount of a structural bone-compatible matrix effective to absorb said gene, wherein said device is capable of stimulating bone formation when implanted within a bone progenitor tissue site of an animal.

68. The device of claim 67, wherein said device is a titanium or a hydroxylapatite-coated titanium device.

69. The device of claim 67, wherein said device is shaped to join a bone fracture site in said animal.

70. The device of claim 67, wherein said device is shaped to fill a bone cavity site in said animal.

71. The device of claim 67, wherein said device is an artificial joint.

72. A method of delivering a nucleic acid segment to a fibroblast cell located within a repair tissue site of an animal, comprising contacting said tissue site with a composition comprising a nucleic acid segment and a structural bone-compatible matrix to effect uptake of the nucleic acid segment into the fibroblast cell and to promote expression of a transcriptional or translational product in said cell.

73. A method of delivering at least one selected nucleic acid segment to a fibroblast cell located within a repair tissue site of an animal, comprising the steps of:

(a) preparing a matrix-nucleic acid composition comprising at least one nucleic acid segment and a structural bone-compatible matrix; and

(b) contacting said repair tissue site with the structural matrix-nucleic acid composition to effect uptake of the nucleic acid segment by the fibroblast cell, wherein said nucleic acid segment expresses a transcriptional or translational product in said cell.

74. The method of claim 73, wherein said nucleic acid segment is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

75. The method of claim 73, wherein said structural bone-compatible matrix is a collagenous, metal, hydroxylapatite, hydroxylapatite-coated metal, bioglass, aluminate, bioceramic, acrylic ester polymer, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

76. The method of claim 75, wherein said structural bone-compatible matrix is a collagenous matrix.

77. The method of claim 75, wherein said structural bone-compatible matrix is a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix.

EXHIBIT F

Original Claims in Grandparent, Patent No. 5,763,416

1. A method for transferring a nucleic acid segment into bone progenitor cells, comprising contacting bone progenitor cells with a composition comprising a nucleic acid segment so as to transfer said nucleic acid segment into said cells.

2. The method of claim 1, wherein said cells are located within a bone progenitor tissue site of an animal and said tissue site is contacted with said composition so as to promote nucleic acid transfer into bone progenitor cells *in situ.*

3. The method of claim 2, wherein the contacting process comprises bringing said nucleic acid segment into contact with a bone-compatible matrix to form a matrix-nucleic acid segment composition and bringing said matrix-nucleic acid segment composition into contact with said tissue site.

4. The method of claim 1, wherein said nucleic acid segment is a DNA molecule.

5. The method of claim 1, wherein said nucleic acid segment is an RNA molecule.

6. The method of claim 1, wherein said nucleic acid segment is an antisense nucleic acid molecule.

7. The method of claim 1, wherein said nucleic acid segment is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

8. The method of claim 1, wherein said nucleic acid segment encodes a polypeptide or protein that stimulates bone progenitor cells when expressed in said cells.

9. The method of claim 3, wherein said bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer or lactic acid polymer matrix.

10. The method of claim 9, wherein said bone-compatible matrix is a titanium matrix.

11. The method of claim 10, wherein said bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

12. The method of claim 9, wherein said bone-compatible matrix is a collagen preparation.

13. A method of stimulating bone progenitor cells, comprising contacting bone progenitor cells with a composition comprising an osteotropic gene so as to promote expression of said gene in said cells.

14. The method of claim 13, wherein said cells are located within a bone progenitor tissue site of an animal and said tissue site is contacted with said composition so as to promote bone tissue growth.

15. The method of claim 14, wherein the contacting process comprises bringing said osteotropic gene into contact with a bone-compatible matrix to form a matrix-gene composition and bringing said matrix-gene composition into contact with said tissue site.

16. The method of claim 13, wherein said osteotropic gene is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

17. The method of claim 13, wherein said osteotropic gene is a parathyroid hormone (PTH) gene, a bone morphogenetic protein (BMP) gene, a growth factor gene, a growth factor receptor gene, a cytokine gene or a chemotactic factor gene.

18. The method of claim 17, wherein said osteotropic gene is a transforming growth factor (TGF) gene, a fibroblast growth factor (FGF) gene, a granulocyte/macrophage colony stimulating factor (GMCSF) gene, an epidermal growth factor (EGF) gene, a platelet derived growth factor (PDGF) gene, an insulin-like growth factor (IGF) gene, or a leukemia inhibitory factor (LIF) gene.

19. The method of claim 18, wherein said osteotropic gene is a TGF-α, TGF-β1 or TGF-β2 gene.

20. The method of claim 17, wherein said osteotropic gene is a PTH gene.

21. The method of claim 17, wherein said osteotropic gene is a BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 gene.

22. The method of claim 21, wherein said osteotropic gene is a BMP-2 or BMP-4 gene.

23. The method of claim 15, wherein said bone-compatible matrix is a collagenous, metal, hydroxylapatite, bioglass, aluminate, bioceramic, acrylic ester polymer or lactic acid polymer matrix.

24. The method of claim 23, wherein said bone-compatible matrix is a titanium matrix.

25. The method of claim 24, wherein said bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

26. The method of claim 23, wherein said bone-compatible matrix is a collagen preparation.

27. The method of claim 15, wherein said matrix-gene composition is applied to a bone fracture site in said animal.

28. The method of claim 15, wherein said matrix-gene composition is implanted within a bone cavity site in said animal.

29. The method of claim 15, wherein said bone cavity site is the result of dental or periodontal surgery or the removal of an osteosarcoma.

30. A composition comprising a nucleic acid segment in association with a bone-compatible matrix.

31. The composition of claim 30, wherein said nucleic acid segment is a DNA molecule.

32. The composition of claim 30, wherein said nucleic acid segment is an RNA molecule.

33. The composition of claim 30, wherein said nucleic acid segment is an antisense nucleic acid molecule.

34. The composition of claim 30, wherein said nucleic acid segment is a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus.

35. The composition of claim 30, wherein said nucleic acid segment encodes a polypeptide or protein that stimulates bone progenitor cells when expressed in said cells.

36. The composition of claim 30, wherein said bone-compatible matrix is a collagenous, titanium, hydroxylapatite, hydroxylapatite-coated titanium, bioglass, aluminate, bioceramic, acrylic ester polymer or lactic acid polymer matrix.

37. The composition of claim 36, wherein said bone-compatible matrix is a collagen preparation.

38. A composition comprising an osteotropic gene in association with a bone-compatible matrix, said composition being capable of stimulating bone growth when administered to a bone progenitor tissue site of an animal.

39. The composition of claim 38, wherein said osteotropic gene is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus.

40. The composition of claim 38, wherein said osteotropic gene is a PTH, BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, TGF-α, TGF-β1, TGF-β2, FG, GMCSF, EGF, PDGF, IGF or a LIF gene.

41. The composition claim 40, wherein said osteotropic gene is a TGF-α, TGF-β1, TGF-β2, PTH, BMP-2 or BMP-4 gene.

42. The composition of claim 38, wherein said bone-compatible matrix is a collagenous, metal, hydroxyapatite, bioglass, aluminate, bioceramic, acrylic ester polymer or lactic acid polymer matrix.

43. The composition of claim 42, wherein said bone-compatible matrix is a titanium matrix.

44. The composition of claim 43, wherein said bone-compatible matrix is a titanium matrix coated with hydroxylapatite.

45. The composition of claim 42, wherein said bone-compatible matrix is a collagen preparation.

46. An osteotropic device, comprising an osteotropic gene capable of expression in bone progenitor cells, the gene associated with an amount of a bone-compatible matrix effective to absorb said gene, wherein said device is capable of stimulating bone formation when implanted within a bone progenitor tissue site of an animal.

47. The device of claim 46, wherein said device is a titanium or a hydroxylapatite-coated titanium device.

48. The device of claim 46, wherein said device is shaped to join a bone fracture site in said animal.

49. The device of claim 46, wherein said device is shaped to fill a bone cavity site in said animal.

50. The device of claim 46, wherein said device is an artificial joint.